



How radical prostatectomy procedures have changed over the last 10 years in Italy: a comparative analysis based on more than 1500 patients participating in the MIRROR-SIU/LUNA and the Pros-IT CNR study

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Abstract

Purpose Therapeutic strategies for prostate cancer (PCa) have been evolving dramatically worldwide. The current article reports on the evolution of surgical management strategies for PCa in Italy.

Methods The data from two independent Italian multicenter projects, the MIRROR-SIU/LUNA (started in 2007, holding data of 890 patients) and the Pros-IT-CNR project (started in 2014, with data of 692 patients), were compared. Differences in patients' characteristics were evaluated. Multivariable logistic regression models were used to identify characteristics associated with robot-assisted (RA) procedure, nerve sparing (NS) approach, and lymph node dissection (LND).

Results The two cohorts did not differ in terms of age and prostate-specific antigen (PSA) levels at biopsy. Patients enrolled in the Pros-IT-CNR project more frequently were submitted to RA (58.8% vs 27.6%, $p < 0.001$) and NS prostatectomy (58.4% vs. 52.9%, $p = 0.04$), but received LND less frequently (47.7% vs. 76.7%, $p < 0.001$), as compared to the MIRROR-SIU/LUNA patients.

At multivariate logistic models, Lower Gleason Scores (GS) and PSA levels were significantly associated with RA prostatectomy in both cohorts. As for the MIRROR-SIU/LUNA data, clinical T-stage was a predictor for NS (OR = 0.07 for T3, T4) and LND (OR = 2.41 for T2) procedures. As for Pros-IT CNR data, $GS \geq (4 + 3)$ and positive cancer cores $\geq 50\%$ were decisive factors both for NS (OR 0.29 and 0.30) and LND (OR 7.53 and 2.31) strategies.

Conclusions PCa management has changed over the last decade in Italian centers: RA and NS procedures without LND have become the methods of choice to treat newly medium–high risk diagnosed PCa.

Keywords Prostate cancer · Pros-IT CNR study · MIRROR SIU/LUNA study · Robotic procedures · Nerve sparing · Lymph node dissection

Members of The MIRROR-SIU/LUNA Study Group and the Pros-IT CNR Study Group are listed in Acknowledgements section.

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Introduction

Treatment pathways for prostate cancer (PCa) patients have been evolving dramatically over recent years worldwide, leading to different patterns of surgical strategies throughout the development and improvement of diagnostic and staging tools, such as preoperative nomograms, multidisciplinary guidelines, and the advent of robotic technology.

Intensifying prostate-specific antigen (PSA) screening efforts, lowering PSA threshold for prostate biopsy and the ever-growing number of samples taken have contributed to the rising incidence rates of PCa [1].

Despite these changes, radical prostatectomy (RP) remains the surgical standard treatment for patients with organ confined PCa [2, 3]. Moreover, throughout time, available evidence focused on general topics regarding RP, including the role of robot assisted (RA) procedures, nerve sparing (NS) approach and/or lymph node dissection (LND). Likewise, Internet has become an important source of information for patients on waiting lists for RP, but only 36% of the information provided about PCa treatment is in accordance with the guidelines of the European Association of Urology (EAU) [4]. In addition, there seems to be a low compliance with guidelines by Italian urologists [5].

In 2007, the Italian Urological Association (SIU) with the Leading Urological No-profit Foundation for advanced Research (LUNA—Fondazione SIU Onlus) instituted the Multicenter Italian Report on Radical prostatectomy Outcome and Research (MIRROR), involving 136 Urology Departments located throughout the country [6]. In 2014, the PROState cancer monitoring in Italy, from the National Research Council (Pros-IT CNR) study, prospective, multicenter project monitoring PCa patients attending 97 Urology, Radiation therapy, and Oncology Departments located throughout Italy, was instituted [7].

The aim of this retrospective observational study was to analyze and compare data from the two PCa patients' cohorts, mostly in terms of RA, NS, and LND rates observed over the 7-year time frame.

Materials and methods

The MIRROR, an independent prospective observational study started in Italy in 2007, aimed to create a register of patient surgically treated for PCa [6]. Overall, consecutive patients, from 2007 to 2011, underwent RP in 136 participating centers. The following information was gathered from all participating patients: age, calculated body mass index (BMI), preoperative tumor characteristics (i.e., serum PSA value, clinical T-stage, and GS at biopsy, number and percent of positive cancer cores). Likewise, patients' preoperative general quality of life (QoL) was evaluated using the validated translation of the Short Form Health Survey (SF-12) [8]; their PCa-specific QoL was evaluated using the validated translation of the University of California Los Angeles-Prostate Cancer Index (UCLA-PCI) [9]. The surgical data (RA vs. non-RA RP; NS vs. non-NS; LND vs. no LND) have also been collected.

The Pros-IT CNR is an ongoing, prospective, multicenter study, aimed at monitoring the QoL of a sample of Italian

treatment-naïve males diagnosed with biopsy-verified PCa after September 1st 2014. Overall, patients who met study's eligibility criteria were enrolled in the 97 participating centers (51 Urology, 39 Radiation Oncology, 7 Medical Oncology) [7]. Baseline questionnaire was administered at the time of PCa diagnosis, and follow-up evaluations were planned for a 60-months period [10, 11]. The data on patients' demographics, BMI, comorbidities, initial diagnosis, and cancer staging (i.e., PSA levels, clinical T-stage, biopsy GS, details regarding the prostate biopsy) were collected. Patients' general and PCa-specific QoL at diagnosis were evaluated using the SF-12 and UCLA-PCI questionnaires. Only data from patients who underwent RP and whose QoL records were complete entered this analysis. The surgical data (robot-assisted vs. non-robot assisted RP; NS vs. non-NS; LND vs. no LND) have also been collected and eventually analyzed.

Both projects, in accordance with the principles of the Declaration of Helsinki, were approved by the Ethic Committee of both coordinating centers and of each participating center. All participants provided their informed consent.

RA RP was performed using either the Si or Xi da Vinci robotic platform in a four-arm configuration, according to centers availability. Trendelenburg tilt was set at 30° in all cases. All procedures were performed according to general principles and surgical details, previously described [12].

Both Pros-IT CNR and MIRROR data were analyzed without imputation of missing data. The normality of distributions was tested using the Shapiro–Wilk test. The data are presented as either means and standard deviation (SD) of the mean, or medians and interquartile ranges for quantitative variables, and as frequencies and percentages for categorical variables. The differences in terms of patients' characteristics between the two cohorts were assessed using the Chi-square or the Fisher's exact test and the Wilcoxon rank-sum test.

Multivariable logistic regression models were applied to identify the characteristics associated with the use of (a) RA, (b) NS approach, and (c) LND in both cohorts. Each model was adjusted for age at diagnosis (years), BMI (obesity vs normal weight, underweight or overweight), T staging at diagnosis (T1 vs T2 or T3-T4), GS at diagnosis (3+3 vs 3+4, 4+3, 8+), serum PSA at diagnosis (< 10 vs 10–20 or > 20 ng/mL), the percentage of positive cores, and D'Amico risk classification (low vs intermediate or high risk) [13]. The models were also adjusted for general and PCa-specific QoL scores at diagnosis, dichotomized with respect to the third quartile (Q3) of their distribution. Significance was set for a *p* value < 0.05. Analyses were performed using SAS 9.4 statistical software.

Results

Overall, the data of 890 patients (37%) for the MIRROR and 692 (40.6%) for the Pros-IT CNR cohort, respectively, who underwent RP and whose QoL information were recorded, were finally analyzed.

Patients' age at diagnosis, median PSA level at biopsy, mean BMI and waist circumference value were not different between the two groups (Table 1). Conversely, Pros-IT CNR cohort had a lower clinical T-stage in a greater rate

of patients compared to MIRROR cohort (cT1 for 54.3% vs 45%; $p < 0.0001$, respectively), but higher biopsy GS (GS 8–10 in 14.2% vs 10.1%; $p < 0.0001$, respectively). Similarly, Pros-IT CNR cohort had a higher mean number of cores at biopsy (14.3 ± 4.6 vs 12.6 ± 4.1 , $p < 0.0001$, respectively, with a median of 12 for each cohort) and higher median percentage of positive cores (33 vs 29; $p = 0.0123$, respectively) as compared to MIRROR cohort.

Pros-IT CNR patients showed higher mean scores on the physical component summary (PCS) of the SF-12 and on the urinary function (UF) ($p < 0.0001$), the bowel

Table 1 Patient data and disease characteristics

	MIRROR ($n=890$)	Pros-IT CNR ($n=692$)	p
Patient's characteristics			
Age (years) (mean \pm SD)	64.9 \pm 6.5	64.6 \pm 6.7	0.3316
BMI (kg/m^2)			
Mean \pm SD	26.4 \pm 3.2	26.5 \pm 3.2	0.4869
Underweight ^a (n , %)	0 (0.0)	2 (0.3)	0.3966
Normal weight ^a (n , %)	252 (35.1)	226 (32.9)	
Overweight ^a (n , %)	383 (53.3)	368 (53.6)	
Obese ^a (n , %)	83 (11.6)	90 (13.1)	
Waist circumference (cm) (mean \pm SD)	94.3 \pm 14.9	93.0 \pm 12.1	0.2358
Preoperative tumor features			
Clinical stage (n , %)	<0.0001		
cT1	385 (45.0)	371 (54.3)	
cT2	418 (48.8)	259 (37.9)	
cT3, cT4	45 (5.3)	35 (5.1)	
PSA at biopsy (ng/mL)			
Median, IQR	7.0 (5.1–9.9)	6.9 (5.2–9.9)	0.9375
< 10, n (%)	669 (75.2)	522 (76.3)	0.6176
10–20, n (%)	158 (17.8)	122 (17.8)	
> 20, n (%)	63 (7.1)	40 (5.9)	
Gleason Grade Groups at biopsy (n , %)	<0.0001		
1	554 (62.7)	334 (48.7)	
2	163 (18.5)	160 (23.3)	
3	77 (8.6)	95 (13.8)	
4	66 (7.5)	67 (9.8)	
5	23 (2.6)	30 (4.4)	
D'Amico risk class (n , %)	0.1580		
Low	276 (33.3)	209 (34.0)	
Intermediate	374 (45.2)	251 (40.8)	
High	178 (21.5)	155 (25.2)	
Bioptical features			
Number of biopsy cores (mean \pm SD)	12.6 \pm 4.1	14.3 \pm 4.6	<0.0001
Percentage of positive cores	0.0123		
Mean \pm SD	34.7 \pm 24.9	36.1 \pm 23.9	
Median, IQR	29 (17–50)	33 (17–50)	
Min, max	0, 100	0, 100	

BMI body mass index, PSA prostate-specific antigen

^aUnderweight: < 18.5 kg/m^2 , normal weight 18.5–24.9 kg/m^2 ; overweight: 25.0–29.9 kg/m^2 ; obese: $\geq 30.0 \text{ kg}/\text{m}^2$

function (BF) ($p = 0.0002$) and the bowel bother (BB) components ($p = 0.0008$) of the UCLA-PCI at diagnosis (Table S1). Conversely, the two cohorts did not differ as far as the mental component summary (MCS) of the SF-12 and the urinary bother (UB), the sexual function (SF) and the sexual bother (SB) components of the UCLA-PCI were concerned.

More robotic procedures were carried out in the Pros-IT CNR than in the MIRROR cohort (58.8% vs 27.6%; $p < 0.0001$; respectively). Nerve sparing approach was more common in the Pros-IT CNR group (57.8% vs 52.9%, $p = 0.0449$): bilateral NS prostatectomy was performed in 42.6% and 36.3% of the Pros-IT CNR and MIRROR cohort, respectively. Less patients in the Pros-IT CNR were submitted to LND than in the MIRROR group (47.7% vs. 76.7%; $p < 0.0001$, respectively).

At logistic regression models (Table S2), the higher was the age at diagnosis, the lower was the probability of being submitted to RA and NS strategies in both cohorts. Advanced age was associated with higher odds of LND procedures only in the MIRROR population. Obesity and the D'Amico risk class were not associated with any outcomes taken into consideration.

Gleason score $> 4 + 3$ at biopsy showed, at multivariable analysis, a value of 0.29 (95% CI 0.13–0.68) for the MIRROR and 0.37 (95% CI 0.18–0.78) for the Pros-IT CNR cohort, respectively. Moreover, the OR related to a serum PSA ≥ 20 ng/mL at diagnosis was 0.20 (95% CI 0.06–0.69) for the MIRROR and 0.40 (95% CI 0.16–1.03) for the Pros-IT CNR cohort, respectively (Table S2). The clinical T-stage did not emerge to be relevant in Pros-IT population as well as the RA strategy was concerned (OR = 1.47, 95% CI 0.50–4.31). Conversely, clinical T-stage was associated with the decision to perform both NS and LND in the MIRROR cohort respect to the Pros-IT group (OR = 0.07, 95% CI 0.01–0.58 for T3–T4 and OR = 2.41, 95% CI 1.36–4.27 for T2) (Table S2). Biopsy GS $\geq 4 + 3$ and a $\geq 50\%$ percentage of positive cores was associated with the decision to perform NS (OR = 0.29, 95% CI 0.14–0.62 and OR = 0.37, 95% CI 0.23–0.59, respectively) as well as LND (OR = 7.53, 95% CI 3.40–16.7 and OR = 2.31, 95% CI 1.45–3.69, respectively) in the Pros-IT CNR cohort of patients.

Regarding the QoL, lower score on the physical component of the SF-12 scale emerged to be a protective factor against RA only in the MIRROR population (OR = 0.53, 95% CI 0.31–0.92). Scores for the SF and SB components of the UCLA-PCI at diagnosis below the third quartile were associated with RA RP in the MIRROR cohort (SF OR = 2.17, 95% CI 1.13–4.16) and with the LND in the Pros-IT CNR one (SB OR = 2.14, 95% CI 1.24–3.69).

Discussion

It is well established that PCa should be managed on a personalized basis [3] and that the surgical strategy and approach should be determined on the basis of the patient's demographic and clinical characteristics. The frequency of minimally invasive approaches reflects all the important technological advancements that have recently taken place in the field of urology [14, 15] and dramatically changed the management of PCa patients. In fact, 3D magnification, Endowrist technology and the use of RA surgery have enabled surgeons to develop improved techniques in Urology.

The analysis of our data showed that both cohort of patients shared similar characteristics (i.e., age, BMI, waist circumference, and median serum PSA value) (Table 1). Therefore, we sought to investigate whether some preoperative variables could have been differently associated with the surgical decision over the 7-year time frame that separated patients' enrollment between the two studies. In this context, parallel multivariate analyses were carried out (Table S2).

A first relevant finding was that the number of RA and NS procedures increased (27.6–53.4% and from 52.9 to 57.8%, in the two cohorts, respectively), whereas the frequency of the LND fell down (76.7% vs. 47.7%, respectively). A further analysis also uncovered that selection criteria for robotic surgery were mainly based on tumor-related (i.e.; GS and PSA) rather than patient-related characteristics (i.e.; SF-12 PCS and age). In this context, surgeons' experience, skill, and confidence with the RA approach seemed to be important factors when intermediate and high-risk patients were considered.

Furthermore, the comparison between the two projects (separated by a 7-year time lag) showed that clinical T-stage, once considered a crucial step for choosing both RA and NS approaches, is no longer relevant; in contrast GS at biopsy, once ignored when the NS and LND strategies were being contemplated, is now one of the main determinants.

As for LND procedures, GS at biopsy and the percentage of positive cores seemed to be the most important factors considered. Of clinical relevance, the most recent project (i.e., Pros-IT CNR) depicted that patient's age was no longer a determinant for LND compared to seven years before [16, 17].

Our findings are in agreement with evidence currently available. Although the decision to perform LND was not based on a validated nomogram [18, 19], the single elements considered by our multivariable models are all included in the most popular nomograms available. Indeed, the decision to consider single elements rather

than a nomogram seemed particularly appropriate given the long study period (7 years), the many changes made in those nomograms and the different weight of each factor [16, 17, 20]. This feeling can be further illustrated by referring to the Briganti nomogram which predicts lymph node involvement in prostate cancer patients. According to that model, if a 5–10 ng/ml PSA range predicts an increase of only 10 points, the clinical T-stage and GS at biopsy are both considered important elements in predicting lymph node involvement.

Our data have confirmed the results of the Martini-Clinic database that showed that GS, serum PSA levels, and the number of positive biopsy cores were independent predictors for LND in both open and RA RP in high-volume centers [21]. Moreover, even if PSA has kept its importance in terms of surgical decision, the percentage of positive cores at biopsy has become even more relevant both for NS and LND.

These results could be linked to advancements in the technical accuracy of robotic surgery and the more precise preoperative imaging assessment tools—including magnetic resonance [22], fusion biopsy [23], 3D technology [24], etc.—that are increasingly being used to evaluate patients with PCa.

It should be noted that the significantly higher mean number of biopsy cores in Pros-IT CNR population might be related to the wide time period of the studies, during which methods and number of cores significantly changed.

Despite the significant reduction in palpable tumors (cT2: 48.8% vs. 37.9%) found by the most recent survey (Pros-IT CNR), men at the same age and with the same PSA value showed the comparable median number of positive cores at biopsy (i.e., 12), although they presented different percentages of positive cores (33% vs. 29%). The changes occurred over time in the guidelines about prostate biopsies (namely, indications, procedures, and interpretation of results) have led to a dramatic increase in high grade PCa in the latter as compared to the former cohort of patients (GS \geq 8: 14.2% vs. 10.1%, respectively) and a concomitant reduction in the number of indolent or low grade PCa (GS = 6: 48.7% vs 62.7%, respectively).

Of further clinical relevance the finding that the D'Amico risk class was not associated with the surgical decisions at multivariate analyses in both cohorts. This quite unexpected result might be linked to the higher impact of single oncologic features (such as grade, stage, and PSA) with respect to risk classes referring to a combination of variables [25]. In addition, criteria for RA procedures have probably changed over the last 10 years. In fact, general and cancer-specific QoL analyses have demonstrated that nowadays candidates for RA RP seem to be more fit and to have better urinary and bowel control. On the contrary, patients with urinary and/or bowel dysfunction are being offered other treatment options

[6, 26–28]. Similarly, it is also possible that patients' expectations in terms of urinary function after RP are currently higher than those reported only 10 years ago [6, 26–28].

Finally, while none of the projects seemed to take obesity into consideration during preoperative assessments, in accordance with current literature reports, the Pros-IT study found a further reduction in terms of the OR for the obese patients to be finally considered for RA, NS prostatectomy and LND compared to the MIRROR cohort (1.0 vs. 1.8, 0.6 vs. 0.8 and 0.7 vs. 2.0, respectively) [29, 30].

The present study is not devoid of limitations. First of all, we compared the populations of two different studies with dissimilar designs, number of patients per center, proposed objectives and methods. Second, since PCa patients in the two groups were treated both at referral as well as at minor urologic centers, current findings may not be considered generalizable. Nevertheless, both used the same tests to evaluate patients' general and PCa-related QoL. Moreover, selection criteria for robotic surgery are based on tumor-, patient-, center- and surgeon-related factors. Owing to the primary aims of the studies, these data are not totally available, and they are not considered in our analysis. However, the selection criteria listed above, are partially related to surgeon decision-making and maybe they are not entirely generalizable. Key factor for the specific purpose of the analyses, the studies referred to two different time frames, an important issue when robotic technology is being discussed. These limitations may have affected data's homogeneity and generalizability. Finally, the lack of information on long-term outcomes can be considered a further methodological bias.

Despite these limitations, the multi-institutional experiences outlined here provide a revealing snapshot of the Italian trend to use RA RP in case of organ-confined PCa, highlighting patient and tumor related factors that continue to be considered relevant when surgical options (RA, NS and LND) are contemplated.

Overall, the current findings confirm that PCa management has dramatically changed over the past single decade, mostly because of newly developed therapeutic technologies [31]. Our study presents a picture of surgical treatments of PCa in a specific country over a specific timeframe. Future studies will be able to: assess the impact of the surgeon's experience and skill; evaluate very long-term functional and oncological outcomes after robotic vs. open surgery; pinpoint criteria for selecting candidates who most could benefit from a minimally invasive approach; and compare various therapeutic options for PCa and the differences attained in low and high volume centers.

To conclude, major technological advancements have been fully incorporated in the practice of Italian urologists, aiming at reducing the toxicity of the surgical treatment and possibly ameliorating outcomes; hopefully, future breakthroughs in surgical techniques and preoperative assessment

tools will lead to even better outcomes for patients underwent RP.

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